Allelic Loss in Esophageal Squamous Cell Carcinoma Patients with and without Family History of Upper Gastrointestinal Tract Cancer

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ABSTRACT

Chromosomal regions with frequent allelic loss may point to major susceptibility genes that will assist in understanding molecular events involved in esophageal carcinogenesis. Esophageal squamous cell carcinoma samples and blood from 46 patients, including 23 patients with and 23 patients without a family history of upper gastrointestinal cancer, were screened using laser microdissected DNA and tested for loss of heterozygosity (LOH) at 18 marker loci representing 14 chromosomal regions (on 2q, 3p, 4p, 4p, 5q, 6q, 8p, 9p, 9q, 11p, 13q, 14q, 15q, and 17p) identified in an earlier genome-wide scan to have frequent LOH. Clinical/pathological and lifestyle risk factor data were also collected. For all 46 tumors combined, the lowest frequency LOH for any of the 18 markers was 37%, and 8 markers showed LOH in ≥75% of informative tumors. One marker (*D13S894* on 13q) showed greater LOH in patients with a positive family history (93% *versus* 50%; $P = 0.04$), whereas two markers (*D6S1027* on 6q and *D9S910* on 9q) had significantly more LOH in patients with metastasis, and one marker (*D4S2361* on 4p) showed significantly higher LOH in patients with a lower pathological tumor grade. No relation was seen between LOH and lifestyle risk factors. This study confirms the previously observed high frequency LOH for these 14 chromosomal regions, including a locus on 13q where LOH is more common in patients with a family history of upper gastrointestinal cancer than in those without such history, suggesting that a gene in this area may be involved in genetic susceptibility to esophageal cancer.

INTRODUCTION

Esophageal squamous cell carcinoma is one of the most common fatal cancers worldwide. There is great geographic variation in the occurrence of this tumor, including exceptional high risk areas such as Shanxi province, a region in north central China with some of the highest esophageal cancer rates in the world (1–4). Although epidemiological studies indicate that tobacco and alcohol are the major risk factors for esophageal cancer in the low-risk regions of Europe and North America, the etiology in high-risk areas remains less clear. Several possibilities, including nitrosamines, nutritional deficiencies, fermented and moldy foods, and the exposure to polycyclic aromatic hydrocarbons have been considered, but none have been convincingly linked to Shanxi's high rates of esophageal cancer (5). Previous studies in this high-risk region have, however, demonstrated a strong tendency toward familial aggregation (6–10), suggesting that genetic susceptibility may play a role in the etiology of esophageal cancer.

The molecular events associated with the initiation and progression of esophageal squamous cell carcinoma remain poorly understood, although frequent allelic deletions and other genetic abnormalities affecting individual tumor suppressor genes have been detected in these tumors (11, 12). Chromosomal regions with frequent allelic loss may point to major susceptibility genes that will assist in understanding molecular events involved in esophageal carcinogenesis and serve as the basis for the development of markers for genetic susceptibility testing and screening for the early detection of this cancer.

To better understand the genetic changes involved in the development of esophageal cancer and ascertain potential susceptibility genes, we had previously conducted a genome-wide scan in 11 esophageal squamous cell carcinoma patients with a family history of upper gastrointestinal cancer (*i.e.*, esophageal or stomach cancer) using 366 microsatellite markers. In that scan, 14 chromosomal regions were identified by 46 markers having very high frequency (≥75%) LOH.[2,3] The study reported here expands our efforts to understand the role of genetics in the etiology and prevention of esophageal cancer in the

Received 4/30/99; revised 8/23/99; accepted 8/27/99.
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[2] The abbreviation used is: LOH, loss of heterozygosity.

[3] N. Hu, M. Roth, M. Polymeropolous, Z. Z. Tang, M. R. Emmert-Buck, Q. H. Wang, A. M. Goldstein, S. S. Feng, S. M. Dawsey, T. Ding, Z. P. Zhuang, X. Y. Han, T. Ried, C. Giffen, and P. R. Taylor. Identification of novel regions of allelic loss from a genome-wide scan of esophageal squamous cell carcinoma in a unique high-risk Chinese population, submitted for publication.